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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,274	10/15/2001	Chrisotpher John Robert Thomas	9341-028-999	4439

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EXAMINER	
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ART UNIT	PAPER NUMBER
1638	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/978,274	THOMAS ET AL.	
	Examiner	Art Unit	
	Medina A. Ibrahim	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-55 and 57-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-55 and 57-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/21/07 has been entered.

Claims 46-55 and 57-69 are pending and are examined.

Claim Objections

Claim 52 is objected to for failing to further limit parent claim 51. The Pro-PAP-S protein does not further limit SEQ ID NO: 2 because the specification indicates that Pro-PAP-S cannot be other than SEQ ID NO: 2.

At claims 51, 58, and 66-69, it is suggested that " a pro-PAP-S protein, a mature PAP-S protein, or a PAP-S α protein, and a PAP-S β protein be replaced with SEQ ID NO: 2, 4, 6, and 8, respectively, for clarification. In addition, according to the specification, a pro-PAP-S protein, a mature PAP-S protein, or a PAP-S α protein, and a PAP-S β protein cannot be other SEQ ID NO: 2, 4, 6, and 8, respectively.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 68-69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 68-69 are indefinite because "the PAP-S α protein" and "the" PAP-S β protein lack antecedent basis in claim 46. If Applicant intends ---wherein the pokeweed antiviral protein is PAP-S α protein (or PAP-S β protein), the claim should be amended to recite as such.

Claim Rejections - 35 USC § 112

Claims 46-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing nematode resistance in a transgenic plant by introducing a chimeric gene comprising the pokeweed antiviral protein (PAP) encoding sequences of SEQ ID NO: 1, 5, or 7 under the control of a nematode inducible promoter in a transgenic plant and SEQ ID NO: 3 in transgenic potato plants, and plants and plant cells produced by said method, does not reasonably provide enablement for a method of inducing cell death in any plant cells with any pokeweed encoding nucleic acids.

The claims are drawn to a method of inducing cell death in specific cells of a plant, said method comprising exposing a plant comprising a chimeric gene comprising a nucleic acid encoding pokeweed antiviral protein including Pro-PAP-S (SEQ ID NO: 2), PAP-S (SEQ ID NO: 4), PAP-S α (SEQ ID NO: 6) and PAP-S β (SEQ ID NO: 8), and a pathogen or chemical inducible promoter, wherein the expression of said pokeweed antiviral protein induces cell death in said specific cells. The claims are also drawn to

said nucleic acid hybridizes under stringent conditions to SEQ ID NO: 1, 3, 5 or 7 and encodes PAP capable of inducing cell death. The claims are also drawn to a molecule comprising a DNA encoding PAP-S α or PAP-S β a plant produced by said method.

Applicant teaches constructs containing PAP-S nucleic acid sequences encoding SEQ ID NO: 2, 4, 6, and 8 under the control of 35S CaMV or a nematode inducible promoter for transient assay in tobacco protoplasts to show PAP-S mediated ribosome inactivation (Figures 5-7). Applicant also teaches transformation of tobacco and potato with said constructs and expression of Pro-PAP-S or mature PAP-S in nematode infected root cells. Applicant teaches transformation of tobacco with Pro PAP-S encoding sequence and potato plants with mature PAP-S or Pro-PAP-S sequences resulted in transgenic tobacco and potato plants with nematode resistance (Figures 13-14). Applicant teaches that transformation of tobacco cells with a nucleic acid encoding mature PAP-S (SEQ ID NO: 4) failed to produce transformed tobacco cells showing that the mature PAP-S sequence does not function in tobacco plants.

Applicant does not provide guidance for a method of inducing cell death in nay specific cells in any plant species using exemplified or non-exemplified pokeweed encoding nucleic acids with exemplified or non-exemplified inducible promoters. Applicant has not taught that pokeweed antiviral proteins can function in any cells of any plant species. The prior art does not provide predictability in using any PAP to produce plants with desired phenotype. In addition, the instant specification does not provide guidance for inducible promoters that are also cell-specific other than nematode

inducible promoters of KNT1 or RB7 that function with any PAP encoding nucleic acids in transgenic plants.

Nielson et al (Annu. Rev. Plant Physiol. Plant Mol. Biol. (2001), vol. 52, pp. 785-816, in record) teach about ribosome inactivating proteins including pokeweed, their enzymatic activities, and their complex biological role. Nielson et al specifically states that while plant RIPs have been linked to antiviral, antifungal and insecticidal activity in transgenic plants, the mechanism of these effects remains unresolved (see at least the Abstract on page 785). The paragraph bridging pages 801 and 802, the cited reference states "(a)lthough the enzymatic mechanism of RIP activity is well defined, the physiological steps by which ribosome inactivation leads to cell death are not well understood".

The prior art teaches that transformation of a plant with a PAP encoding nucleic acids is highly unpredictable. For example, Lodge et al (PNAS, vol. 90, pp.7089-7093, 1993, Applicant's IDS) teach that the expression of PAP in transgenic plants may result undesired phenotype such as stunted, molted and sterility in the plant. Lodge et al teaches that tobacco plants expressing high levels (above 10ng/mg of protein) of wild type and mutant PAP tend to have stunted and mottled phenotype, and some the plants were sterile (see page 7090, Results and Discussion). On the other hand, Barbieri et al (Biochemica et Biophysica Acta, vol. 1154, pp. 237-282, 1993, Applicant's IDS) teaches that plant RIPs including PAP can act on their ribosome only at high levels of concentrations (see pages 251-252, section III-A). Another example is Tumer et al (PNAS, vol. 94, pp. 3866-3871, 1997, Applicant's IDS) who teach transgenic tobacco

plants expressing high levels of PAP with point mutations showed growth reduction and lesions on their leaves (Fig. 3 on page 3868), while transgenic plants expressing high levels of active site mutant PAP didn't show antiviral activity, and while transgenic plants expressing low levels of C-terminal deletion mutant were resistant to virus and showed normal growth (Table 2, page 3870).

In addition, the working examples disclosed in the specification are limited to the use of nucleic acids encoding pro-PAP-S (SEQ ID NO: 2), mature PAP-S (SEQ ID NO: 4), PAP-S α (SEQ ID NO: 6), and PAP-Sβ (SEQ ID NO: 8) in potato and tobacco. The ability of pro-PAP-S, PAP-S α and PAP-S β in tobacco and potato, and SEQ ID NO: 3-4 in potato to induce cell death in specific cells cannot be extrapolated to all PAP encoding sequences, absent further guidance.

Therefore, given the breadth of the claims, the state of the prior art; the nature of the invention; the limited working examples, and the unpredictability with respect to PAP activity in transgenic plants as discussed above, the claimed invention is not enabled throughout the broad scope. See In re Wands 858 F.2d 731, 8USPQ2nd 1400 (Fed. Cir, 1988).

Response to Arguments

Applicant correctly states that the test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. Applicant, however, maintains that all pending claims in this application satisfy the enablement requirement of 35 USC 112, 1st paragraph. Applicants specifically argue against

Examiner's comments regarding the inability to transform tobacco with nucleic acids encoding the mature PAP-S and Applicants submit that they were able to generate transgenic tobacco and potato plants expressing Pro-PAP-S (SEQ ID NO: 2) at the site of nematode feeding which led nematode size resistance using the same methods disclosed in the specification (response, p. 10).

These are not found persuasive because Applicants' arguments are not commensurate with the scope of the claims. While Applicants have demonstrated expression of Pro-PAP-S in transgenic potato and tobacco, the specification clearly shows that with repeated experiments, transformation of tobacco with the SEQ ID NO: 3 encoding SEQ ID NO: 4 (mature PAP-S) failed to yield transgenic shoots as expected showing. Therefore, there is unpredictability inherent in expressing pokeweed antiviral proteins in transgenic plants. Applicant provides no convincing evidence to the contrary. In addition, claims drawn to a method that employs with SEQ ID NO: 1-2 are not rejected.

Applicant also argues that the instantly claimed invention provides a solution to the problems of using PAP with either the constitutive promoter, or with low level expression of PAP which resulted in undesirable phenotype in the transgenic plants disclosed by Lodge and Turmer or Barbieri cited by the Examiner (response, p. 10).

This is not found persuasive because using PAP with a nematode inducible promoter also failed to produced transgenic tobacco plants as shown in Applicant's own working examples. Applicant's working example shows that expression of the mature PAP-S gene under the control of a nematode inducible promoter failed to produce

transgenic tobacco plants. Examples in WO 99/60843 (Applicant's IDS) show that transgenic tobacco expressing PAP under the control of CaMV 35S can be produced. Therefore, there is unpredictability inherent in expressing pokeweed antiviral proteins in transgenic plants. Applicant provides no convincing evidence to the contrary.

In *Genentech Inc. v. Novo Nordisk* A/S (42 USPQ2d 1001 at p. 1005) The CAFC stated "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not workable...While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention...[W]hen there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required.... It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". Id. In this case, as in *Genentech*, the specification does not provide the "reasonable detail .....to enable members of the public to understand and carry out the invention" as broadly claimed.

Given that the broad scope of the claims encompassing a method that employs any and all nucleic acids encoding pokeweed antiviral protein; the limited working examples; the unpredictability inherent in expressing PAP in a transgenic plant as evidenced by Lodge et al; Barbieri et al; and Applicant's own specification teaches that a method for expressing a mature PAP-S under the control of a inducible promoter failed to produce transgenic tobacco plant; and the complex biological function of RIPs

as discussed above, the claimed invention is not enabled throughout the broad scope. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 46, 50, 54-55, 57, and 59-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tumer et al (WO 99/60843, Applicant's IDS) in view of Thomas et al (US 6,140,554).

The claims are drawn a method of inducing cell death in specific cells of a plant, said method comprising exposing a plant comprising a chimaeric gene comprising a

nucleic acid molecule encoding a pokeweed antiviral protein, and an inducible promoter which induces expression of said protein in said specific cells, upon exposing said plant to a pathogen or chemical or which is cell type specific, wherein the expression of said PAP induces cell death in said specific cells of said plant. The claims encompass regenerating transformed cells expressing said chimaeric gene.

Tumer et al teach a method of producing transgenic plants expressing a chimeric gene comprising a nucleic acid encoding pokeweed antiviral protein designated as PAP II, including full length, wild type and a truncated protein PAP II with deleted C-terminal, operably linked to a promoter expressible in plant cells; said promoter can be a pathogen inducible or tissue-specific for expression of said promoter in tissue-special manner or inducible by a pathogen. Transgenic plants expressing pokeweed antiviral protein having viral and fungal resistance are also disclosed (pages 16-23). The cited reference also teaches that the nucleic acids encoding PAPII can be used to induce nematode resistance using in a transgenic plant (page 9, 1st full paragraph). The cited reference further teaches different promoters that can be used to express PAP in transgenic plants and their availability in the prior art; promoters include wound-induced, specific cell types (such as leaf epidermal cells, meosphyll cells, root cortex cells), specific tissues or organs types (roots, leaves or flowers, for example); light-induced or other temporally-regulated promoter, or chemically regulated promoters.

Tumer et al do not explicitly teach a nematode inducible promoter.

Thomas et al teach methods of producing nematode resistant transgenic plants using cell-specific promoters such as KNT1 and RB7. At the paragraph bridging

columns 4 and 5, Thomas et al teach the importance of using feeding cell-specific promoters with cell-death system to disrupt the nematode feeding cells. The nematodes include *Meloidogne javanica* (see columns 4-7).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of transforming a plant with a pokeweed antiviral protein encoding DNA to induce viral or fugal resistance as taught by Tumer et al, and to modify that method by incorporating any of the inducible promoters known in the prior art such as KNT1 or RB7 taught by Thomas et al, without unexpected results. One would have been motivated to use any of the PAPs known in the prior with any of the known promoters, given the antiviral, antifungal disease and nematode resistance activity by PAP protein in transgenic plants as taught and suggested by Tumer et al. One would have been motivated to use feeding-cell promoters such as KNT1 or RB7 given that they are well characterized and have been successful used in construct to induce nematode resistance in transgenic plants as taught by Thomas et al, and given the problem of nematodes in crop production as taught by Thomas et al and as known to one of ordinary skill in the art. Therefore, the claimed invention as whole was clearly a *prima facie* obvious.

Claims 46-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over each of Tumer et al (WO 99/60843, Applicant's IDS) and Kanieswski et al (6, 015, 940 in view of Thomas et al (US 6,140,554) and Poyet et al (FEBS (1997) vol 409 no.1-2, pp. 97-100).

The claims are drawn a method of inducing cell death in specific cells of a plant, said method comprising exposing a plant comprising a chimaeric gene comprising a nucleic acid molecule encoding a pokeweed antiviral protein, and an inducible promoter which induces expression of said protein in said specific cells, upon exposing said plant to a pathogen or chemical or which is cell type specific, wherein the expression of said PAP induces cell death in said specific cells of said plant. The claims are also drawn said method, wherein the nucleic acid is either SEQ ID NO: 1, 3, 5, 7, or nucleic acid that hybridizes thereto under specified hybridization conditions and encodes a proPAP-S, mature PAP-S, PAP-Sά or PAP-S ß that induces cell death, or nucleic acid molecule encoding SEQ ID NO: 2, 4, 6 or 8. The claims are further encompass regenerating transformed cells expressing said chimaeric gene, and nucleic acid molecule comprising DNA encoding SEQ ID NO: 6 or 8 linked to an inducible promoter..

Tumer et al teach a method of producing transgenic plants expressing a chimeric gene comprising a nucleic acid encoding pokeweed antiviral protein designated as PAP II, including full length, wild type and a truncated protein PAP II with deleted C-terminal, operably linked to a promoter expressible in plant cells; said promoter can be a pathogen inducible or tissue-specific for expression of said promoter in tissue-special manner or inducible by a pathogen, and suggest that PAP can also be used to induce nematode resistance as discussed above.

Kanieswski et al teach a method of inducing viral resistance in tobacco and potato plants and plant cells, the method comprising transforming said plants/plant cells with a chimeric gene comprising a DNA sequence encoding PAP' or a mutant thereof

retaining PAP activity, a tissue-specific or inducible promoter, N-terminal signal sequence capable of targeting said PAP' in specific cells of the plant. The reference further teaches transgenic potato plants that are resistant to PVX, PVY and PLRV (potato virus X, Y, and potato leafroll viruses) (column 2; column 9, lines 24-41; Examples 2-3; and columns 27-28). In column 3, lines 2-10 and column 4, lines 3-30, Kanieswski suggests that other forms of PAP including PAP-S and PAP-II can be isolated from pokeweed seed and summer leaf, respectively, and used in the disclosed method. In column 9, lines 25-45, the cited reference suggests expressing the pokeweed antiviral protein in a tissue-specific manner in cells where viral infection is known to occur.

Tumer et al and Kanieswski et al do not explicitly teach a nematode inducible promoter.

Thomas et al teach methods of producing nematode resistant transgenic plants using cell-specific promoters such as KNT1 and RB7. At the paragraph bridging columns 4 and 5, Thomas et al teach the importance of using feeding cell-specific promoters with cell-death system to disrupt the nematode feeding cells. The nematodes include *Meloidogne javanica* as discussed above.

Tumer et al and Kanieswski et al in view of Thomas et al do not explicitly teach PAP-S nucleic acids encoding SEQ ID NO: 2, 4, 6, or 8.

Poyet et al teach isolated and characterized nucleic acids encoding SEQ ID NO: 2, 4, 6, 8 or nucleic acids that hybridize to SEQ ID NO: 1, 3, 5 or 7 and encoding proteins with PAP-S activity.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of transforming a plant with a pokeweed antiviral protein encoding DNA to induce viral or fugal resistance as taught by Tumer et al, and to modify that method by incorporating any of the inducible promoters known in the prior art such as KNT1 or RB7 taught by Thomas et al; without unexpected results. One would have been motivated to use any of the PAPs known in the prior taught by either Tumer et al, Kanieswski et al or Poyet etal, with any known promoter, given the antiviral, antifungal disease resistance activity in transgenic plants as taught by each of Tumer et al, Kanieswski et al or Poyet etal, and nematode resistance activity as suggested by Tumer et al. One would have been motivated to use feeding-cell promoters such as KNT1 or RB7 given that they are well characterized and have been successful used in construct to induce nematode resistance in transgenic plants as taught by Thomas et al, and given the problem of nematodes in crop production as taught by Thomas et al and as known to one of ordinary skill in the art. Therefore, the claimed invention as whole was clearly a *prima facie* obvious.

Remarks

No claim is allowed.

Contact information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Medina A. Ibrahim whose telephone number is (571)

272-0797. The Examiner can normally be reached Monday -Thursday from 8:00AM to 5:30PM and every other Friday from 9:00AM to 5:00 PM. Before and after final responses should be directed to fax nos. (703) 872-9306 and (703) 872-9307, respectively.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov/>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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6/25/07

Mai

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ART UNIT 1638